

Amendments to the Specification

On page 7, line 19 to page 8, line 18, please replace the paragraph beginning "The term "reactive functionality", when used herein" with the following paragraph.

The term "reactive functionality", when used herein for purposes of the specification and claims, means a chemical group or chemical moiety that is capable of forming a covalent bond or bond for operably binding polymer to synthetic peptide. With respect to chemical groups, a reactive functionality is known to those skilled in the art to comprise a group that includes, but is not limited to, maleimide, thiol, carboxy, phosphoryl, acyl, hydroxyl, acetyl, hydrophobic, amido, dansyl, sulfo, a succinimide, a thiol-reactive, an amino-reactive, a carboxyl-reactive, and the like. A chemical moiety may comprise a linker. Linkers are known to refer to a compound or ~~moiety~~ moiety that acts as a molecular bridge to operably link two different molecules (e.g., a wherein one portion of the linker binds to a synthetic peptide, and wherein another portion of the linker binds to the polymer in forming the conjugate according to the present invention). The two different molecules may be linked to the linker in a step-wise manner. There is no particular size or content limitations for the linker so long as it can fulfill its purpose as a molecular bridge. Linkers are known to those skilled in the art to include, but are not limited to, chemical chains, chemical compounds (e.g., reagents), amino acids, and the like. The linkers may include, but are not limited to, homobifunctional linkers, heterobifunctional linkers, biostable linkers, and biodegradable linkers, as well known in the art. Preferably, when a linker is used, it is a non-planar (e.g., so that operably bound synthetic peptide is not rigidly fixed to polymer). Heterobifunctional linkers, well known to those skilled in the art, contain one end having a first reactive functionality to specifically link a first molecule, and an opposite end having a second reactive functionality to specifically link to a second molecule. It will be evident to those skilled in the art that a variety of bifunctional or polyfunctional reagents, both homo- and hetero-functional (such as those described in the catalog of the Pierce Chemical Co., Rockford, Ill.), may be employed as a linker with respect to the present invention. Depending on such factors as the molecules to be linked, and the conditions in which the linking is performed, the linker may vary in length and composition for optimizing such properties as preservation of biological function stability, resistance to certain chemical and/or temperature

parameters, and of sufficient stereo-selectivity or size. For example, the linker should not significantly interfere with the ability of the synthetic peptide (to which it is linked) to function as an inhibitor of either or both of HIV fusion and HIV transmission to a target cell. A preferred reactive functionality may be used, in application to the present invention, to the exclusion of a reactive functionality other than the preferred reactive functionality.

On page 10, line 12 to page 12, line 10, please replace the paragraph beginning "The term "synthetic peptide", in relation to a peptide" with the following paragraph.

The term "synthetic peptide", in relation to a peptide used with the present invention, is used herein for the purposes of the specification and claims to mean peptide (a) produced by chemical synthesis, recombinant expression, biochemical or enzymatic fragmentation of a larger molecule, chemical cleavage of larger molecule, a combination of the foregoing or, in general, made by any other method in the art, and isolated; (b) comprising an amino acid sequence of no less than about 16 amino acids and no more than about 60 amino acid residues in length, and consists of no less than 14 contiguous amino acids found in of either the HR1 region or HR2 region of gp41 of HIV (in which may include one or more amino acid substitutions); and (c) capable of inhibiting transmission of HIV to a target cell (preferably, by complexing to either an HR region of HIV gp41 and/or preventing fusion between HIV-1 and a target cell), as can be determined by assessing antiviral activity *in vitro* and/or *in vivo* as will be described in more detail herein. The term "isolated" when used in reference to a peptide, means that the synthetic peptide is substantially free of components which have not become part of the integral structure of the peptide itself; e.g., such as substantially free of cellular material or culture medium when produced by recombinant techniques, or substantially free of chemical precursors or other chemicals when chemically synthesized or produced using biochemical or chemical processes. The amino acid sequence of the synthetic peptide may comprise one or more amino acid substitutions and/or one or polymorphisms found in the sequence of the relevant region of the HIV gp41, or may comprise one or more amino acid substitutions which are added to stabilize helix structure and/or affect oligomerization so that the peptide self-assembles into a trimer

(see, for example, the disclosure of U.S. application number 10/664,021 _____ which is herein incorporated by reference). Further, the amino acid sequence, in addition to having a core peptide derived from HIV gp41, may comprise one or more enhancers peptides linked to the core peptide, e.g., at the N-terminus, at the C-terminus or at both the N-terminus and C-terminus, or may have a core peptide derived from one or more of HIV-1, HIV-2, and SIV (see, e.g., U.S. Patent No. 6,258,782, the disclosure of which is herein incorporated by reference; see also synthetic peptide comprising the amino acid sequences shown in SEQ ID NOs:5, & 46 to 59). Depending on the synthetic peptide used, the synthetic peptide operably bound to polymer may exist as a monomer, or an oligomeric form such as a trimer. In an example wherein the synthetic peptide exists as a trimer, only a single molecule may be operably bound to the polymer, whereas the rest of the molecules of synthetic peptide comprising the trimer are self-assembled around the operably bound molecule of synthetic peptide. For example, illustrative synthetic peptides comprising HR1 peptides having amino acid substitutions therein (compared to SEQ ID NO:1) which preferably self-assemble into trimers (e.g., a trimer being comprised of three molecules of synthetic peptide) comprise the amino acid sequences shown in SEQ ID NOs:61 to 74. Preferably, the synthetic peptide for application to the present invention may comprise a sequence of no less than about 16 amino acids and no more than about 60 amino acid residues in length, and preferably no less than 36 amino acids and no more than about 51 amino acids in length, and more preferably no less than about 41 amino acids and no more than about 51 amino acids in length. Preferably, for a synthetic peptide comprising sequence derived from the HR1 region of HIV gp41, the synthetic peptide comprises a contiguous sequence of at least amino acid residues 18 to 54 of SEQ ID NO:1 (by single letter designation, NNLLRAIEAQQHLLQL TVWGIKQLQARILAVEYL KD) or polymorphisms thereof, as key determinants in this portion of the HR1 region have been found to influence biochemical and antiviral parameters described herein. Illustrative synthetic peptides derived from the HR1 region include, but are not limited to peptides having the amino acid sequences shown in SEQ ID NOs:3, & 6 to 31. A preferred synthetic peptide derived from the HR1 region may be used in producing a conjugate according to the present invention to the exclusion of an HR1 peptide other than the preferred synthetic

peptide. Preferably, for a synthetic peptide sequence derived from the HR2 region of HIV gp41, the synthetic peptide comprises a contiguous sequence of at least amino acid residues 43 to 51 of SEQ ID NO:2 (e.g., QQEKNEQEL), as key determinants in this portion of the HR2 region have been found to influence biochemical and antiviral parameters described herein. Illustrative synthetic peptides derived from the HR2 region include, but are not limited to peptides having the amino acid sequences shown in SEQ ID NOs:4, 32, 75 to 99, & 114. A preferred synthetic peptide derived from the HR2 region may be used in producing a conjugate according to the present invention to the exclusion of an HR2 peptide other than the preferred synthetic peptide. Numerous of such synthetic peptides that may be applied to the present invention have been disclosed previously in, for example, U.S. Patent Nos. 5,656,480, 6,133,418, and 6,258,782; the disclosures of which are herein incorporated by reference in their entirety). The term "synthetic peptide alone" is used herein, for the purposes of the specification and claims, to mean synthetic peptide not operably bound to polymer; i.e., in an unconjugated form which is devoid of polymer.

On page 17, lines 22 to 32, please replace the paragraph beginning "To the solution of crude compound 5" with the following paragraph.

To the solution of crude compound 5, $\text{PEG}_6\text{-(NH-AA(36-17)-Fmoc)}_2$, (3.0g, not dry) in NMP (10ml) was DBU (100 μ l) added. After stirring at room temperature for 1hr, PL-SO₃H resin (150mg) was added in and continued stirring for 40 minutes. The resin was filtered off and washed by NMP (10ml). The treatment of the NMP solution with H₂O (30ml) resulted in a milk-like emulsion. H₂O (100ml) was added to the emulsion and the mixture was then lyophilized. The resulting yellow sticky oil was suspended with EtOH (10ml), heated to 50°C for 5 minutes, and then cooled down to room temperature. The white slurry was formed upon the addition of H₂O (20ml) and stirred for 30 minutes. The white solid was collected by vacuum ~~filtration~~ filtration and washed by EtOH-H₂O (1:1, 10ml \times 2). The crude compound 6, $\text{PEG}_6\text{-(NH-AA(36-17)-H)}_2$, was dried in vacuum oven (35°C) for overnight.

On page 28, line 19 to page 29, line 13, please replace the paragraph beginning "It is apparent to one skilled in the art" with the following paragraph.

It is apparent to one skilled in the art from the descriptions herein, that where the polymer used in producing a conjugate according to the present invention is polyamino acid-based, that polynucleotides encoding such conjugate may be synthesized or constructed, and that such conjugate may be produced by recombinant DNA technology as a means of manufacture and/or (for example, *in vivo* production) for a method of inhibiting transmission of HIV to a target cell. It is also apparent to one skilled in the art that more than one polynucleotide sequence can encode a conjugate according to the present invention, and that such polynucleotides may be synthesized on the basis of triplet codons known to encode the amino acids of the amino acid sequence of the conjugate, third base degeneracy, and selection of triplet codon usage preferred by the host cell (e.g., prokaryotic or eukaryotic, species, etc.) in which expression is desired. For example, a polymer may comprise polylysine, and lysine may be encoded by any one of the codons AAA, or AAG. In another example, a heteropolymer comprised of lysines and alanines may be used, with alanine being encoded by any one of the codons GCA, GCG, GCC, or GCU. In another example in which one molecule of synthetic peptide is linked to the amino terminus of the polymer and a second molecule of synthetic peptide is linked to the carboxy terminus of the polymer, it may be desired to have a flexible linker which operably binds the molecules of synthetic peptide to the polymer. It is well known in the art that a flexible linker which may be applied to ~~operably~~ operably bind together two amino acid sequences may be comprised of glycine or glycine combined with other amino acids such as serine. Glycine is known to be encoded by any one or more of GGU, GGC, GGA, or GGG; whereas serine is known to be encoded by any one or more of AGU, AGC, UCU, UCC, UCA, or UCG. Illustrative examples may include, but are not limited to, (the number indicating the number of molecules): Gly(3), GlySerGly, Gly(4)Ser(3), GlySer, and the like. A preferred flexible linker may be determined using methods standard in the art. Thus, for example, a conjugate may comprise:
synthetic peptide-flexible linker-polymer-flexible linker-synthetic peptide.